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Prenatal Exposure to Select Phthalates and Phenols and Associations with Fetal and Placental Weight among Male Births in the EDEN Cohort (France)

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Background: The placenta performs crucial physiological functions to ensure normal fetal development. Few epidemiological studies investigated placental weight sensitivity to phthalates and phenols.

Objective: Our goal was to explore whether maternal exposure to select phthalates and phenols is associated with changes in placental weight at birth and in placental–to–birth weight ratio (PFR).

Methods: Placental weight and birth weight were available for 473 mother–son pairs in the EDEN (Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant) cohort for whom 9 phenols (4 parabens, 2 dichlorophenols, triclosan, benzophenone-3, bisphenol A) and 11 phthalate metabolites were measured in spot urine samples collected between weeks 23 and 29 of gestation. We used adjusted Elastic Net penalized regression models (ENET) to select biomarkers associated with placental weight, birth weight and PFR. Unpenalized effect estimates were then obtained by fitting linear regression models simultaneously adjusted for the ENET-selected biomarkers and *a priori* chosen confounders.

Results: The multipollutant ENET model for placental weight retained four biomarkers: triclosan and monocarboxy-isononyl phthalate (MCNP), which were negatively associated with placental weight, and benzophenone-3 and the sum of parabens, which were positively associated with this outcome. The ENET model for PFR retained two phthalate metabolites [MCNP and monocarboxy-isooctyl phthalate (MCOP)], which were negatively associated with this outcome.

Discussion: The positive association between the sum of parabens and placental weight was consistent with results of a previous study among 49 male births. Our results provide preliminary evidence of possible associations between other compounds such as triclosan, benzophenone-3, MCNP, and MCOP and both placental weight and PFR. These associations were not reported in previous studies and should be seen as hypothesis generating. Studies relying on repeated assessments of exposure in prospective mother–child cohorts are needed to substantiate the plausibility of the hypotheses generated by our results. https://doi.org/10.1289/EHP3523

Introduction

Placental Weight and Placental Efficiency

The placenta is the main interface between the mother and the fetus. This organ performs crucial physiological functions such as nutrient, oxygen, and waste transportation during pregnancy (Jansson and Powell 2007). The placenta also produces, metabolizes, and regulates transfer of various hormones such as estrogens, progesterone, and human chorionic gonadotropin (hCG) (Murphy et al. 2006), which are crucial for fetal development. The placental–to–birth weight ratio (PFR) has been used as a proxy measure of placental efficiency with the common idea that decreased PFR reflects increased placental activity and nutrient transfer capacity, whereas increased PFR indicates less efficient placenta (Hayward et al. 2016). U-shaped associations have been observed between PFR and several perinatal outcomes such as fetal death (Haavaldsen et al. 2013) and preeclampsia (Dahlstrøm et al. 2008). Regarding placental weight, both extreme low and high placental weights have been associated with adverse health outcomes. Low placental weight was associated with increased risk of preterm preeclampsia (Dahlstrøm et al. 2008), cryptorchidism (Arendt et al. 2016; Ghazarian et al. 2018) and hypospadias among males at birth (Arendt et al. 2016), whereas high placental weight has been associated with lower Apgar scores at birth (Eskild et al. 2014) and increased risk of term preeclampsia (Dahlstrøm et al. 2008).

Placental Weight Regulation

In toxicological studies, modifications of the environment during pregnancy, such as induced hypoxia, modification of the circulating levels of glucocorticoid and insulin-like growth factors as well as diet restriction, could affect placental weight (Fowden and Forhead 2009). Environmental contaminants might also play a role as suggested by epidemiological studies reporting associations between air pollutants, cigarette smoking, and placental weight (Christianson 1979; Rahmalia et al. 2012; Spira et al. 1975; van den Hooven et al. 2012; Yorifuji et al. 2012). Here, we focused on two other families of contaminants, phenols and phthalates, with prevalent exposure in the general population (Casas et al. 2013; CDC 2014). Data regarding associations between these compounds and markers of placental growth in humans are sparse (Zhu et al. 2018; Ferguson et al. 2018).

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Sources of Exposures to Select Phenols and Phthalates

Several phenols are manufactured in high volume with wide industrial applications. Triclosan is a biocide used in antiseptic wash products (e.g., antibacterial soaps), deodorants, household cleaners, laundry detergents, kitchenware, and some fabrics and toys (Dhillon et al. 2015). Parabens are used as preservatives in cosmetics, personal care products, food, and some pharmaceuticals (Andersen 2008). Benzophenone-3 is an ultraviolet light filter used in sunscreen, clear plastic packaging, and other products to prevent damage to color and scent (e.g., soap, perfumes) (IARC 2013). Bisphenol A is frequently used as the monomer of polycarbonate plastic.

Esters of phthalic acids, commonly called phthalates, are used as plasticizers in polyvinyl chloride plastics, household and car building materials, personal care products, solvents for ink and paints, and some medical devices (Hauser and Calafat 2005).

Associations between Exposure to Phenols and Phthalates and Placental Weight

To our knowledge, only two epidemiological studies, one focusing on phthalates (Zhu et al. 2018) and the other on phenols (Ferguson et al. 2018), examined the associations between environmental exposure to these compounds and markers of placental growth. Zhu et al. (2018) reported associations between maternal urinary concentrations of several phthalate metabolites [mono-butyl phthalate (MBP), mono-methyl phthalate, and di-2-ethylhexyl phthalate (DEHP) metabolites] and placental length, breadth, and thickness among 2,725 pregnant women. Both positive and negative associations were observed depending on the phthalate, timing of exposure (first, second, or third trimester of pregnancy), and sex of the baby (Zhu et al. 2018). Ferguson et al. (2018) assessed exposure to 10 phenols or their precursors (four parabens, triclosan, triclocarban, bisphenol S, two dichlorophenols, and benzophenone-3) and reported decreased placental weight with prenatal exposure to triclosan among girls and increased placental weight with prenatal exposure to butylparaben among boys (Ferguson et al. 2018, 2019). This study had a low sample size with only 49 boys and 42 girls included but not necessarily low validity given the high accuracy of exposure assessment provided by repeated measures of the chemical biomarkers ($n = 3$ urine samples per women).

Objective

We explored the associations between urinary concentrations of phthalate and phenol biomarkers during pregnancy and placental weight and PFR at birth among 473 male newborns. We also reported associations with the weight of the fetuses at birth.

Population and Methods

The EDEN Cohort

We relied on a subgroup of the EDEN (Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant) mother–child cohort, which consists of pregnant women recruited from April 2003 to March 2006 in the obstetrical departments of the university hospitals of Nancy and Poitiers, France. Participation was proposed to all potentially eligible women visiting the prenatal clinics of Nancy and Poitiers university hospitals before their 24th week of gestation [assessed by the date of the last menstrual period (LMP)]. Exclusion criteria were multiple pregnancies, known diabetes before pregnancy, French illiteracy, or planning to move out of the region within the next 3 y (Heude et al. 2016). The cohort was approved by the relevant ethical committees (Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale, Le Kremlin-Bicêtre University hospital, and Commission Nationale de l'Informatique et des Libertés).

Study Population

The current study was restricted to a subgroup of 473 mother–son pairs of the EDEN cohort for which placental weight and information on phenol and phthalate exposure biomarkers during pregnancy were available. Phenol and phthalate metabolite urinary concentrations were only available for mother–son pairs because they were assessed in the framework of a previous project that aimed at investigating the associations of these compounds on male congenital malformations (Chevrier et al. 2012).

Main Outcomes: Placental Weight, Birth Weight and PFR

Placental and birth weight were obtained at birth from hospital maternity records (Rahmalia et al. 2012). Placental weight was not collected as part of the original cohort protocol and is not recorded systematically in French maternity clinics, and the frequency of this measure differed between our two recruitment centers (missing for 43% of births in Nancy compared with 7% of births in Poitiers). PFR was computed as $[\text{placental weight (g)}/\text{birthweight (g)}] \times 100$.

Quantification of Phenol and Phthalate Biomarkers

Women were asked to collect a sample of their first morning urine at home before the first study visit, which occurred at the hospital between 23 and 29 gestational weeks. Women who did not collect their urine at home collected a spot sample at the hospital during the visit ($n = 66$, 14%). Urine samples were aliquoted and stored at -80°C before shipment on dry ice to the National Center for Environmental Health laboratory at the CDC in Atlanta, Georgia. The analysis of blinded specimens at the CDC laboratory was determined not to constitute engagement in human subjects research.

Urinary concentrations of 11 phthalate metabolites, including {mono(3-carboxypropyl) phthalate (MCPP), MBP, mono-isobutyl phthalate (MiBP), monobenzyl phthalate (MBzP), monoethyl phthalate (MEP), monocarboxy-isononyl phthalate (MCNP), monocarboxy-isooctyl phthalate (MCOP), and four metabolites of DEHP [mono(2-ethylhexyl) phthalate (MEHP), mono(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono(2-ethyl-5-carboxypentyl) phthalate (MECPP)]}; nine phenols (two dichlorophenols, bisphenol A, benzophenone-3, triclosan and four parabens); and creatinine, a marker of urine dilution, were assessed at the CDC as described in detail in previous publications (Silva et al. 2007; Ye et al. 2005).

Biomarker Concentrations, Imputation and Standardization

Instrumental reading values were used to replace biomarker concentrations below the limit of detection. Instrumental reading values equal to zero (i.e., indicative of no signal) were replaced by the lowest instrumental reading value provided for a given analyte divided by the square root of 2.

We standardized the biomarker concentrations on sampling conditions before analysis using a two-step standardization method based on regression residuals (Mortamais et al. 2012). This standardization consisted of *a*) studying the associations between each sampling condition and the measured biomarker concentrations using adjusted linear regression models, and *b*) using the estimated effects of sampling conditions that were associated with urine concentrations ($p < 0.2$) and the measured biomarker concentrations to predict the concentrations that would have been obtained if all women had collected their urine sample under the same conditions. The sampling conditions considered

were hour of sampling, day of sampling, year of sample analysis at the CDC, gestational age at collection, duration of storage at room temperature before freezing, and creatinine concentration. This standardization has been used in previous publications (Botton et al. 2016; Philippat et al. 2014).

We computed the molar sums (micromoles per liter) of the two dichlorophenols ($\sum$ dicholorophenols), the four parabens ($\sum$ parabens), and the four DEHP metabolites ($\sum$ DEHP), which were strongly correlated within each group (see Table S1). The other biomarkers were studied individually.

Adjustment Factors

Adjustment factors were the same for all outcomes and were chosen *a priori*, including variables likely to be common causes of both the exposures and the outcomes without being likely consequences thereof and factors that were possible predictors of the outcomes only. The selected factors were gestational duration (linear and squared terms), maternal prepregnancy weight (broken stick model with a knot at 60 kg) and height (continuous), maternal age (continuous), maternal active (never, 1–5, ≥6 cigarettes per day) and passive smoking during pregnancy (yes/no), maternal education level (high school or less, up to 2 y after high school, ≥3 y after high school), parity (0, 1, ≥2) and recruitment center (Nancy, Poitiers). Gestational duration was estimated using the date of LMP or gestational duration assessed by the obstetrician if it differed from the LMP-based estimate by more than 2 weeks (Philippat et al. 2012). Our analysis was restricted to those having nonmissing values for these adjustment factors (Table 1 shows the frequency of missing values).

Selection Bias Correction

The high frequency of missing placental weight in Nancy (43% of the births) compared with Poitiers (7%) led to an overrepresentation of women from Poitiers, who were less likely to smoke and were on average older compared with the original EDEN cohort (*p*-values for Pearson's chi-squared or Wilcoxon rank-sum test ≤0.2; Table 1). To correct this overrepresentation that may lead to selection bias, we used inverse probably weighting (IPW). IPW assigns a weight to each participant equal to the inverse of the probability of being included in the analysis (Hernán and Robins 2018). We computed the probability of being included using a logistic regression model adjusted for predictors of both placental weight missingness and placental weight (Hernán and Robins 2018), specifically, recruitment center, mode of delivery (normal or cesarean vs. assisted), months of delivery (July/August vs. rest of the year), reanimation at birth (yes/no), gestational duration (linear + squared term), active (never, 1–5, ≥6 cigarettes per day) and passive (yes/no) smoking, maternal age (continuous), maternal education level (high school or less, up to 2 y after high school, ≥3 years after high school), and parity (0, 1, ≥2). IPW was used in all of our analyses.

Main Statistical Analysis

We used adjusted Elastic Net (ENET)–penalized regression models to detect which biomarker concentrations were associated with placental weight, birth weight, or PFR, simultaneously taking into account all biomarker concentrations. ENET is a penalized regression model relying on a weighted mixture of the least absolute shrinkage and selection operator (LASSO) and ridge penalties. The LASSO penalty allows variable selection through shrinkage. The lowest regression coefficients, corresponding to the least informative predictors, are attributed a zero value and only the most informative predictors are retained by the model. The ridge penalty accommodates correlated exposures and shrinks regression coefficients from correlated predictors proportionally toward zero (Agier et al. 2016; Lenters et al. 2014). The overall penalty (λ) and the mixing proportion for the LASSO and ridge penalties (α) of our ENET model were determined by minimizing the prediction root mean squared error (RMSE) using 10-fold cross validation. To ensure a stable selection of the α and λ parameters, we repeated this cross validation 100 times (Lenters et al. 2016). Given the exploratory character of our analysis (only two previous studies have explored the associations between environmental exposure to phenols and phthalates and placental weight) we used the λ_{min} value (a value that gives the minimum mean cross-validated error), which is supposed to lead to less parsimonious variable selection than λ_{1se} (largest value of lambda that gives an error within 1 standard error of the minimum). We used the R package *glmnet*. To obtain final effect estimates for each outcome that were not shrunken, we fitted a linear regression model that was simultaneously adjusted for all exposure variables selected by ENET plus our set of *a priori* confounders (Lenters et al. 2016). We report all associations retained by the ENET model, without regard to the *p*-values of the unpenalized effect estimates.

Sensitivity Analyses

In sensitivity analyses, we estimated center-specific effects by adding interaction terms between the selected biomarker concentrations and center into the unpenalized linear regression model. For comparison with previous publications, we performed the classical approach that consists of running one linear regression per outcome and exposure in combination with a false-discovery rate (FDR) correction (Benjamini and Hochberg 1995). Each outcome was considered separately for the FDR correction. We referred to this approach as the EWAS (exposome-wide association study) approach.

To check that our results were not driven by extreme values of IPW, we ran an analysis where the extreme low and high values of IPW were assigned the values of the first (extreme low) or the 99th (extreme high) IPW percentile.

To draw our conclusion we gave more weight to associations that were previously described in the literature, namely the positive associations between parabens (Ferguson et al. 2018, 2019), MBP, and DEHP metabolites (Zhu et al. 2018) with placental growth markers.

All analyses were performed using R (version 3.3.1; R Development Core Team) and STATA/SE (version 14; StataCorp.).

Results

Population

Among the 473 mother–son pairs, average gestational age at delivery [plus or minus the standard deviation ($\pm$SD)] was 39.8 weeks $\pm$1.50, average birth weight was 3,373 g $\pm$ 477, average placental weight at birth was 545 g $\pm$ 111, and mean PFR was 16.2 $\pm$ 2.79 (Table 1). Pearson correlation coefficients were 0.58 for placental weight and birth weight, −0.16 for birth weight and PFR, and 0.71 for placental weight and PFR. Just over half (52%) of the women in the study had completed at least 2 y of education after high school and 45% of the women included were nulliparous. Most of the women (85%) did not smoke during pregnancy.

Phenol and Phthalate Metabolite Urinary Concentrations

Frequency of detection of phenols and phthalate biomarkers ranged from 71% to 100% (Table 2). Compared with the mothers from the EDEN cohort with biomarker concentrations but missing placental weight, the concentrations of 2,5 dichlorophenol;

Table 1. Characteristics of live singleton male births from the EDEN (Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant) cohort who were included and excluded from the present analysis.

Characteristic	Included ($N = 473$)		Excluded ($N = 525$)		p-Values[a]
	n (%) or mean ± SD		n (%) or mean ± SD		
Recruitment center					<0.001
Poitiers	326	(69)	207	(39)	
Nancy	147	(31)	318	(61)	
Mode of delivery					0.59
Normal	345	(73)	366	(70)	
Assisted	49	(10)	61	(12)	
Caesarean	79	(17)	96	(18)	
Missing			2	(0)	
Parity					0.54
0	215	(45)	221	(42)	
1	172	(36)	202	(38)	
≥2	85	(18)	102	(19)	
Missing	1	(0)	0	(0)	
Maternal education					0.93
<2 y after high school	220	(47)	239	(46)	
High school + 2 y	102	(22)	117	(22)	
≥High school + 3 y	143	(30)	154	(29)	
Missing	8	(2)	15	(3)	
Maternal BMI (kg/m^2)					0.63
<18.5	45	(10)	47	(9)	
≥18.5 to <25	294	(62)	340	(65)	
≥25	125	(26)	126	(24)	
Missing	9	(2)	12	(2)	
Active smoking during pregnancy					
No	402	(85)	426	(81)	0.14
Yes	71	(15)	97	(18)	
Missing	0	(0)	2	(0)	
Passive smoking during pregnancy					<0.001
No	357	(75)	330	(63)	
Yes	115	(24)	188	(36)	
Missing	1	(0)	7	(1)	
Maternal age (y)	29.6	± 4.86	29.0	± 4.95	0.10
Gestational duration (weeks)[b]	39.8	± 1.50	39.5	± 2.07	0.33
Birth weight (g)	3,373	± 477	3,309	± 584	0.25
Placental weight (g)	545	± 111	537[d]	± 146	0.31
PFR[c]	16.2	± 2.79	16.5[d]	± 3.30	0.39

Note: Male births included in the present study were restricted to those with non-missing placental weight and assessments of phenols and phthalate metabolites in urine. BMI: body mass index, PFR: placental–to–birth weight ratio; LMP, last menstrual period; SD: standard deviation.
[a]Categorical variables: Pearson's chi-squared p-values; continuous variables: Wilcoxon rank-sum test p-values.
[b]Based on the date of the LMP, or gestational duration assessed by the obstetrician if it differed from the LMP-based estimate by more than 2 weeks.
[c]PFR = [placental weight(g)/birthweight(g)] × 100.
[d]$n = 281$ because, among the boys not included, only 281 had a placental weight reported.

sum of dichlorophenols; triclosan; methyl, ethyl, and propyl paraben; sum of parabens; and low-molecular-weight phthalate metabolites (MEP, MBP, MiBP) were lower in our study population (p-values for Wilcoxon rank-sum test <0.10). No difference was observed for the other biomarkers (p-values for Wilcoxon rank-sum test ≥0.18; Table 2).

We observed Spearman correlation coefficients >0.5 between the concentrations of the two dichlorophenols, the four parabens, the four DEHP metabolites, as well as between MBP and MCPP, which are both metabolites of di-*n*-butyl phthalate (MCPP being also a metabolite of di-*n*-octyl phthalate and other high-molecular-weight phthalates). Correlation coefficients between the other biomarker concentrations were lower than 0.45 (see Table S1).

Associations between Phthalate and Phenol Exposure Biomarkers and Placental Weight, Birth Weight, and PFR

Among the 13 exposure biomarkers studied, the sum of parabens, triclosan, benzophenone-3, and MCNP were retained by the multipollutant ENET model for placental weight (Table 3). Spearman correlation coefficients between these four biomarkers were all ≤0.20 (see Table S1). Unpenalized effect estimates obtained from the regression model simultaneously adjusted for these four biomarkers were positive for the sum of parabens {β = 7.12 g [95% confidence interval (CI): 0.41, 13.9] for a 1-unit increase in the ln-transformed concentration} and benzophenone-3 [β = 4.76 g (95% CI: −1.77, 11.3)] and negative for triclosan [β = −4.11 g (95% CI: −8.26, 0.05)] and MCNP [β = −10.9 g (95% CI: −21.8, 0.09)] (Table 3).

Regarding birth weight, benzophenone-3 was the only biomarker selected by the multipollutant ENET model. The associated unpenalized effect estimate was 21.0 g (95% CI: −3.45, 45.5) (Table 3).

The ENET model for PFR selected two biomarkers: MCOP and MCNP (Table 3). The corresponding unpenalized effect estimates were −0.23 (95% CI: −0.58, 0.11), and −0.20 (95% CI: −0.54, 0.13), respectively. The Spearman correlation coefficient for MCOP and MCNP was 0.42.

Sensitivity Analyses

Results of the sensitivity analysis in which the extreme low and high values of IPW were assigned the values of the first or the 99th IPW percentile were similar to those of the main analysis (i.e., the same compounds were selected by ENET; see Table S2).

Results of the EWAS analysis were similar for birth weight and PFR to those of our main analysis relying on ENET (see

Table 2. Urinary phenols and phthalate metabolite concentrations among mother–son pairs of the EDEN (Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant) cohort with ($N = 473$) and without ($N = 131$) placental weight information.

			Study population Percentiles (μg/L[a])				Mothers of the EDEN cohort with biomarker concentrations but missing placental weight Percentiles (μg/L[a])				
Analyte	LOD (μg/L)	% >LOD	*n*	5th	50th	95th	*n*	5th	50th	95th	*p*-Values[b]
Phenols											
2,4-DCP	0.2	98	473	0.23	0.95	9.00	131	0.35	1.01	8.39	0.20
2,5-DCP	0.2	100	473	1.67	9.04	279	131	2.84	11.8	227	0.09
∑DCP (μmol/L)	—	—	473	0.01	0.06	1.78	131	0.02	0.08	1.44	0.08
BPA	0.4	99	473	0.83	2.34	9.76	131	0.86	2.37	7.86	0.53
BP3	0.4	92	473	0.22	2.23	79.4	131	0.12	2.32	69.1	0.94
TCS	2.3	79	473	0.15	25.5	686	131	1.27	30.9	750	0.03
MP	1	100	473	7.52	100	1232	131	9.39	150	1515	0.04
EP	1	71	473	0.08	3.11	65.4	131	0.08	4.69	68.7	0.02
PP	0.2	99	473	0.40	12.0	263	131	0.84	18.5	226	0.02
BP	0.2	85	473	0.09	1.63	57.6	131	0.09	2.13	57.6	0.34
∑PB (μmol/L)	—	—	473	0.06	0.82	10.2	131	0.06	1.41	11.8	0.04
Phthalates											
MEP	0.6	100	473	21.2	94.0	713	131	28.8	133	968	0.04
MBP	0.2	100	473	11.7	43.4	454	131	15.5	49.7	423	0.07
MiBP	0.2	100	473	11.8	39.4	170	131	15.1	48.9	175	0.01
MBzP	0.3	100	473	4.47	18.2	100	131	5.25	19.3	114	0.30
MCPP	0.2	100	473	0.68	1.97	10.0	131	0.72	1.91	9.14	0.68
MEHP	0.5	98	473	1.30	7.40	33.7	131	1.44	7.69	38.1	0.48
MEHHP	0.2	100	473	6.41	27.7	98.5	131	7.25	25.6	116	0.95
MEOHP	0.2	100	473	5.28	22.9	81.6	131	6.39	21.2	90.6	0.68
MECPP	0.2	100	473	12.0	38.9	156	131	13.1	37.9	169	0.64
∑DEHP (μmol/L)	—	—	473	0.09	0.33	1.19	131	0.10	0.31	1.37	0.70
MCOP	0.2	100	473	1.17	3.86	17.4	131	1.31	4.21	20.3	0.18
MCNP	0.2	99	473	0.49	1.26	10.2	131	0.56	1.34	10.9	0.69

Note: —, not applicable; LOD, Limit of detection; 2,4-DCP, 2,4-dichlorophenol; 2,5-DCP, 5-dichlorophenol; BP, butyl paraben; BP3, benzophenone 3; BPA, bisphenol A; EP, ethyl paraben; MBP, mono-*n*-butyl phthalate; MBzP, monobenzyl phthalate; MCNP, monocarboxyisononyl phthalate; MCOP, monocarboxy-isooctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MECPP, mono(2-ethyl-5-carboxypentyl) phthalate; MEHHP; MEHHP, mono(2-ethyl-5-hydroxyhexyl) phthalate; MEHP, mono(2-ethylhexyl) phthalate; MEOHP and MECPP; MEOHP, mono(2-ethyl-5-oxohexyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; MP, methyl paraben; PP, propyl paraben; TCS, triclosan; ∑DCP, molar sum of dichlorophenols; ∑DEHP, molar sum of MEHP; ∑PB, molar sum of parabens (methyl-, ethyl-, propyl- and butylparaben).
[a]Concentrations are given in μg/L for all compounds but the sums of dichlorophenols, of parabens, and of DEHP metabolites.
[b]*p*-Values for the Wilcoxon rank-sum test.

Table S3). Benzophenone-3 was positively associated with birth weight, whereas MCOP and MCNP were negatively associated with PFR. Only two biomarkers (the sum of parabens and MCNP) were associated with placental weight ($p < 0.1$; see Table S3) compared with the four (the sum of parabens, MCNP, benzophenone-3 and triclosan) selected by ENET (Table 3). None of the associations highlighted in this sensitivity analysis remained significant after FDR correction; the lowest corrected *p*-value was 0.39 (see Table S3).

All *p*-values for interactions between center and biomarker concentrations were above 0.2 (see Table S4), except for triclosan and benzophenone-3 in the model on placental weight (p for interaction = 0.02 and 0.06, respectively). In analyses stratified by center, triclosan was not associated with placental weight in Poitiers ($\beta = 0.05$ g (95% CI: −4.72, 4.83; $n = 315$), whereas in Nancy ($n = 142$) each 1-unit increase in the ln-transformed triclosan concentration was associated with a −9.72 g (95% CI: −17.8, −1.58) decrease in placental weight. Similarly, benzophenone-3 was not associated with placental weight in Poitiers [$\beta = -0.04$ g (95% CI: −7.57, 7.49)] but was positively associated with this outcome in Nancy [$\beta = 6.27$ g (95% CI: −4.83, 17.4)].

Discussion

Previous studies reported that butylparaben (Ferguson et al. 2018, 2019) and MBP and DEHP metabolites (Zhu et al. 2018) were positively associated with placental weight, whereas our findings based on data from 473 male births support a positive association between summed parabens and placental weight but no associations with MBP, DEHP, and placental weight. Some novel associations were also suggested: we observed positive associations between benzophenone-3 and placental weight, whereas MCNP and triclosan were negatively associated with this outcome. MCNP and MCOP were negatively associated with PFR, whereas benzophenone-3 was positively associated with birth weight. The fact that the direction of the associations with placental weight differed across biomarkers with some exhibiting positive (the sum of parabens, benzophenone-3) and other negative (triclosan, MCNP) associations with placental weight might reflect different mechanisms of action.

Sum of Parabens

We observed a positive association between the sum of parabens and placental weight. This positive association is in agreement with previous findings among 49 mother–son pairs that reported increased placental weight with prenatal exposure to butylparaben (Ferguson et al. 2018, 2019). In the study by Ferguson et al. (2018) each paraben was studied separately, whereas in our study we used the molar sum of the four parabens. The molar sum limited the number of comparisons done but prevented us from providing an effect estimate per paraben. A study exploring associations between maternal urinary concentration of parabens and placental DNA methylation reported a decrease in the methylation of a region coding for a growth factor involved in both placental and fetal growth [Insulin Growth Factor differentially methylated region (*IGF2*-DMR2) (LaRocca et al. 2014)].

To our knowledge, this is the first study exploring the associations between parabens and PFR. Regarding birth weight, four

Table 3. Associations of phenol and phthalate metabolite concentrations with birth weight, placental weight, and placental–to–birth weight ratio (PFR).

	Penalized effect estimates			Unpenalized effect estimates								
				Birth weight (g)			Placental weight (g)			PFR[a]		
Analyte	Birth weight (g)	Placental weight (g)	PFR[a]	β	95% CI	*p*-Values	β	95% CI	*p*-Values	β	95% CI	*p*-Values
Phenols												
∑DCP (μmol/L)	0	0	0	—	—	—	—	—	—	—	—	—
BPA (μg/L)	0	0	0	—	—	—	—	—	—	—	—	—
BP3 (μg/L)	2.52	0.65	0	21.0	(−3.45; 45.5)	0.09	4.76	(−1.77; 11.3)	0.15	—	—	—
TCS (μg/L)	0	−0.44	0	—	—	—	−4.11	(−8.26; 0.05)	0.05	—	—	—
∑PB (μmol/L)	0	1.74	0	—	—	—	7.12	(0.41 ; 13.9)	0.04	—	—	—
Phthalate metabolites												
MEP (μg/L)	0	0	0	—	—	—	—	—	—	—	—	—
MBP (μg/L)	0	0	0	—	—	—	—	—	—	—	—	—
MiBP (μg/L)	0	0	0	—	—	—	—	—	—	—	—	—
MBzP (μg/L)	0	0	0	—	—	—	—	—	—	—	—	—
MCPP (μg/L)	0	0	0	—	—	—	—	—	—	—	—	—
∑DEHP (μmol/L)	0	0	0	—	—	—	—	—	—	—	—	—
MCOP (μg/L)	0	0	−0.04	—	—	—	—	—	—	−0.23	(−0.58; 0.11)	0.18
MCNP (μg/L)	0	−4.76	−0.04	—	—	—	−10.9	(−21.8; 0.09)	0.05	−0.20	(−0.54; 0.13)	0.23

Note: Both the penalized estimates from the multipollutant elastic net (ENET) penalized regression model and the estimates from the unpenalized linear regression models for the biomarkers selected by ENET are presented. Parameters are reported for an increase by 1 in the ln-transformed biomarker concentration. $N = 457$ mother–son pairs of the EDEN (Etude des Déterminants pré et postnatals du développement et de la santé de l'Enfant) cohort. Data were restricted to mother–son pairs with no missing value for covariates. All models were adjusted for gestational age, maternal active and passive smoking, maternal age, weight and height, maternal education, parity, and recruitment center. We used inverse probability weighting to correct for the overrepresentation of women from Poitiers. The cross-validated optimum ENET tuning parameters were $\alpha = 0.49$, $\lambda_{min} = 25.8$ for birth weight; $\alpha = 0.48$, $\lambda_{min} = 5.94$ for placental weight; and $\alpha = 0.55$, $\lambda_{min} = 0.17$ for PFR. —, not applicable; BP3, benzophenone 3; BPA, bisphenol A; CI, confidence interval; MBP, mono-*n*-butyl phthalate; MBzP, monobenzyl phthalate; MCNP, monocarboxyisononyl phthalate; MCOP, monocarboxy-isooctyl phthalate; MCPP, mono(3-carboxypropyl) phthalate; MEP, monoethyl phthalate; MiBP, mono-isobutyl phthalate; PFR, placental–to–birth weight ratio; TCS, triclosan; ∑DCP, molar sum of dichlorophenols; ∑DEHP, molar sum of MEHP, MEHHP, MEOHP and MECPP; ∑PB, molar sum of parabens (methyl-, ethyl-, propyl- and butylparaben).
[a]PFR = [placental weight(g)/birthweight(g)] × 100.

studies, like ours, did not report any association (Ferguson et al. 2018; Wu et al. 2017; Geer et al. 2017; Aker et al. 2018), whereas one suggested a nonsignificant increase in birth weight in association with prenatal exposure to parabens among boys of the EDEN cohort (Philippat et al., 2014).

Triclosan

We observed a negative association of triclosan with placental weight. In the sensitivity analysis by center, the association was observed in Nancy but not in Poitiers center. Negative association between triclosan and placental weight has been previously reported; however, the association was sex specific and only observed among girls (Ferguson et al. 2018, 2019). In mice, lower placental weight at gestational day (GD) 19 has been reported in the group exposed to triclosan (GD 6 to 18, 8 mg/kg per day) compared with controls. No effect was observed at lower doses (1 and 4 mg/kg per day) (Cao et al. 2017). *In vitro* studies also suggested that triclosan induced cytotoxic, antiproliferative and apoptotic effects on human placental cell lines (Honkisz et al. 2012). Findings from these epidemiological, toxicological, and *in vitro* studies all suggest that triclosan could negatively affect placental weight; however, the inconsistency between the two recruitment centers observed in our study and the fact that Ferguson et al. (2018) reported an association among girls, whereas ours is among boys, warrant investigation in other cohorts.

Triclosan was not clearly associated with either birth weight or PFR in our study population. To our knowledge, this is the first study exploring the association between triclosan and PFR. Regarding birth weight, three previous studies reported no association with triclosan (Geer et al. 2017; Lassen et al. 2016; Philippat et al. 2014), while two reported a negative association (Etzel et al. 2017; Ferguson et al. 2018). Negative associations have also been reported between triclosan and other growth markers, specifically, birth length (Etzel et al. 2017), and head circumference at birth (Etzel et al. 2017; Lassen et al. 2016; Philippat et al. 2014).

Benzophenone 3

We observed a positive association between benzophenone-3 and both placental weight and child birth weight. The association with placental weight was center specific and only observed among mother–son pairs from Nancy.

No association was observed between benzophenone-3 and placental weight in the study by Ferguson et al. (2018) and, to our knowledge, no other study has considered this association. Regarding birth weight, in agreement with our results, a positive association between benzophenone-3 and birth weight was reported among 367 mother–child pairs from New York City (Wolff et al. 2008), whereas two other studies with sample sizes of 459 (Ferguson et al. 2018) and 564 (Tang et al. 2013) reported null associations.

Phthalates

Our results for phthalates were not in line with previous findings; the phthalates associated with placental size in the study by Zhu et al. (2018) were not associated with placental weight in our study. Differences across studies included the markers of placental growth used. We relied on placental weight and PFR, whereas Zhu et al. (2018) studied placental length, breadth, and thickness but not placental weight.

We observed a negative association between two other phthlate metbolites (MCNP and MCOP) and PFR. These metabolites were not measured in the study by Zhu et al. (2018), preventing results comparisons. Given the lack of epidemiological data and the fact that MCNP and MCOP were, with MCPP, the phthalate metabolites with the lowest median concentrations in our study population, our results regarding any associations with PFR need to be replicated.

Strengths

This study is one of the first exploring the associations between environmental exposure to phenols and phthalates and placental weight. Strengths of this study included *a*) the sample size [473 boys, compared with 49 in the previous study on phenols

(Ferguson et al. 2018)], *b*) the number of biomarkers assessed (20), and *c*) the use of ENET to select exposure variables associated with the outcomes. In a setting with some correlations between exposures, compared with the classical EWAS approach in which each exposure is considered separately, ENET is supposed to limit on-average FDR (Agier et al. 2016). In practice, in our study population, no association remained significant in our EWAS sensitivity analysis, whereas a few biomarkers were selected with ENET. Discrepancies between the two approaches might come from the fact that FDR correction applied in the EWAS approach considers all associations as independent without taking into account correlations between exposures and between outcomes to correct for the effective number of tests.

Limitations

In a context of weak and possible sex-specific associations, we considered that an approach restricted to a single sex was preferable over two analyses of about half the original sample size stratified on sex. Restricting our analysis to boys prevents generalization of our findings to girls, but is not a source of selection bias. Selection bias usually occurs when conditioning the study participation on a common effect of the exposure and the outcome [or a collider of the exposure and the outcome (Hernán and Robins 2018)], but sex is not a consequence of any of our outcomes. The high frequency of missing placental weight in Nancy led to an underrepresentation of mother–son pairs from this recruitment center in our study population compared with the original EDEN cohort. To limit the risk of selection bias, this underrepresentation was corrected using IPW. We assessed placental weight and were missing other placental characteristics such as placental diameter, thickness, shape, and vascularization, which are also important for the regulation of the exchanges between the mother and the fetus. A delay in the weighing of the placenta after delivery is likely to cause a lower weight estimate because blood will gradually leak from the placenta. Unfortunately, we did not have access to the time elapsed between placenta expulsion and weighing and were not able to study the impact of this delay on our results. We measured phenols and phthalate metabolites in a single spot urine sample collected during pregnancy. Given the strong within-subject variability of the studied chemicals (Adibi et al. 2008; Philippat et al. 2013; Vernet et al. 2018) and the likely episodic nature of the exposures, our results are expected to be affected by exposure misclassification. However, if, as is likely, exposure measurement error is of classical type, it should have led to effect estimates that were biased towards the null and to loss of power, without expected increase in type 2 error (Perrier et al. 2016). Finally, although minimized by the use of ENET, the risk of chance findings existed (Agier et al. 2016), which is why we gave more weight to the association previously reported in the literature in the results interpretation.

Conclusions

We observed an association between several phenols and phthalate metabolites and both placental weight (MCNP, triclosan, sum of parabens, benzophenone-3) and birth weight (benzophenone-3). The positive association between sum of parabens and placental weight was consistent with findings reported by a previous study for butylparaben and placental weight in 49 male newborns, while the other associations were not consistent with previous studies and thus should be seen as hypothesis generating. The inconsistency between the two recruitment centers observed in our study for some associations (triclosan, benzophenone-3, and placental weight), the low sample size of the previous epidemiological study reporting a similar association for parabens, and the fact that this is one of the first report of associations between the other biomarkers and placental weight and PFR call for cautious interpretation of the results. Additional studies relying on repeated assessments of exposure in prospective mother–child cohorts are needed to substantiate the plausibility of the hypotheses generated by our study.

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